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Individual capacity for repair of DNA damage and potential uses of stem cell lines for clinical applications: a matter of (genomic) integrity

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ABSTRACT

Public and private human stem cell banking institutions are currently hosting hundreds of thousands partially characterized cell populations, including a significant number of human pluripotent stem cell lines. To be considered for use in clinical applications, stem cell preparations must undergo rigorous testing in order to ensure safety for the recipient. With development of the methodologies for in vitro derivation, ex vivo maintenance and expansion of stem cells and targeted differentiation of multipotent and pluripotent stem cells, many novel issues were added to the list of safety concerns of cell and tissue preparations. These issues are related to the potential changes that may occur in the course of in vitro propagation of stem cells and cell-derived products, how these changes may affect the quality of the preparation; and the potential effects on the recipient. Only a limited number of studies about the role of subtle variations of individual capacity for repair of genotoxic damage in maintenance in vitro of human stem cells are currently available. Nevertheless, the assessment of individual repair capacity may play a crucial role in the safety of use of human stem cells, as it constitutes a major factor in the risk of occurrence of genomic alterations that may seriously compromise the quality of the product. This article reviews the available data about the role of individual capacity for DNA damage repair in different human stem cell types and the potential adverse effects that may occur with the use of cell preparations with inferior repair capacity.

Abbreviations: AMD: age-related macular degeneration; DSB: double-strand break; ERCC2: excision repair cross-complementation group 2; ESC: embryonic stem cell; GVHD: graft-versus-host disease; HPSC: haematopoietic stem cell; iPSC: induced pluripotent stem cell; MSC: mesenchymal stem cell; NHEJ: non-homologous end joining; XPC: xeroderma pigmentosum complementation group C; XPD: xeroderma pigmentosum complementation group D; XRCC1: X-ray repair cross-complementing protein 1; XRCC3: X-ray repair cross-complementing protein 3

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Individual capacity for repair of genotoxic damage as a marker of the proliferation and differentiation capacity of stem cells

Cell therapy has become a legitimate therapeutic tool for haematological disease, inherited metabolic disorders, autoimmune disease, some types of solid tumours such as neuroblastoma, and, lately, for multiple sclerosis refractory to other types of treatment [1–5]. Safety for the recipient has always been a crucially important part of the criteria used to assess the potential of cell preparations for clinical applications. This includes not only concerns about the risk of potential transmission of infectious agents, but also short-term effects such as survival of transplanted cells in the recipient, engraftment capability, capacity for rapid restoration of lost function and acute immunity-mediated effects such as acute graft-versus-host disease (GVHD); and long-term effects such as lifespan of the transplanted cells, self-renewing capacity of the stem cell niche, maintenance of production of differentiated cells, risk of recurrence of the primary disease (especially in autologous transplantations), risk of development of secondary disease (usually, neoplasia originating from the transplanted cells) and chronic immunity-mediated effects (chronic GVHD and others). With development of the methodologies for in vitro derivation, ex vivo maintenance and expansion of cells and targeted differentiation of multipotent and

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pluripotent stem cells, a whole host of other issues was added to the list of safety concerns of cell and tissue preparations. These issues are related to the potential changes that may occur in the course of in vitro propagation of stem cells and cell-derived products, how these changes may affect the quality of the preparation; and the potential effects on the recipient.

The proliferation potential of stem cells is typically higher than the potential of somatic cells (although the magnitude may significantly vary). Nevertheless, cultured stem cells may age and/or may be susceptible to carcinogenic transformation. The former may result in lower survival, lower engraftment rates, poor restoration of function and/or secondary disease (e.g. aplastic anemia originating from transplanted cells); whereas the latter may significantly increase the risk of secondary cancer in the recipient. Already, there have been reports about failure to sustain hematopoietic engraftment after transplantation of ex vivo expanded haematopoietic stem cells (HPSCs), development of secondary malignancies in patients with transplanted HPSCs and human pluripotent cell lines prone to genomic instability with potentially oncogenic genomic rearrangements after repeated passaging [6–9].

Detection and repair of genotoxic damage/maintenance of genomic integrity is critically important for progression through the cell cycle. For non-transformed somatic cells, cells that fail to comply with the requirements of the major genomic integrity checkpoints of the cell cycle (predominantly, the G1/S checkpoint) are forced into replicative senescence and/or apoptosis. Stem cells are inherently vulnerable to genotoxic damage for a variety of reasons. Among these, prominent are the 'relaxed' state of the chromatin and the fact that the main damage checkpoint in G1/S may not be functioning at its full efficiency in cells of early embryos (and, respectively, embryonic stem cells [ESCs]) [10,11]. Therefore, cells of early embryos and ESCs that have sustained damage may be routed to programmed cell death but may also be induced to differentiate, as differentiated cells typically have a functioning G1/S checkpoint [11–13]. The propensity of embryonic cells to sustain genomic damage is at least partly overcome by increased efficiency of the DNA repair machinery and activation of specific mechanisms for maintenance of genomic integrity in embryonic cells, such as *Filia*-dependent activation of Parp-1 [12,14,15]. There are, however, genetic factors that determine the individual parameters of the efficiency of DNA repair. There is some degree of inter-individual variance in the capacity to detect and repair DNA damage even among clinically healthy individuals [16,17]. This variance may become significant with age (whether normal aging of the organism or aging of cultured cells), in conditions of increased genotoxic stress (e.g. after genotoxic treatments) and may be associated with adverse effects on the viability, proliferation and differentiation capacity of cells and cell products that may potentially be used for transplantation purposes. Several dozens of polymorphisms in key genes coding for products functioning in DNA repair/maintenance of genomic integrity have already been described (analyzed in detail in [17]). Alone or in combination with other factors, carriership of these polymorphisms may increase the risk of degenerative disease and/or cancer. When one or more of these polymorphisms are present in stem cell preparations intended for transplantation in human patients, it is possible that their otherwise subtle effects on the phenotype may become significant. It may be advisable to include molecular analysis of the capacity to detect and repair DNA damage in the panels for analysis of safety of cell and cell-derived preparations for transplantation purposes.

There have been a couple of studies about the role of efficiency of DNA repair for genomic stability in cultured lymphocytes showing that carriership of variant alleles of common polymorphisms in lymphocytes grown in vitro was associated with increased rates of chromosomal instability [18,19]. The amount of experimental data about the role of genetic polymorphisms of DNA repair genes in the risk of development of transplant-related complications is still limited.

Role of individual repair capacity for the outcomes of treatments based on HPSC

At present, the type of stem cells most commonly used for transplantation purposes are HPSCs and, respectively, the largest body of safety data pertains to HPSC transplantations. Transplantations of HPSCs are often preceded by ablation of the host haematopoiesis (myeloablative conditioning) and are followed by immunosuppressive treatments. Conditioning regimens typically include high-dose genotoxic agents that have severe adverse effects on tissues and organs other than the bone marrow, especially in tissues where cells have rapid natural turnover such as the skin and the gastrointestinal tract. The recovery may therefore be protracted and serious complications such as GVHD arise in no less than 35% of the recipients [20]. Acute GVHD results predominantly from the genotoxic damage inflicted by the pre-transplantation conditioning and its grade may be correlated with survival (typically, higher-

grade acute GVHD is associated with shorter survival). Chronic GVHD arises as a result of the attack of the immunocompetent cells in the graft on the recipient's tissues and may be associated with longer survival [21]. Subtle deficiencies in the capacity to manage genotoxic damage may be at least partly responsible for the risk of development of acute high-grade GVHD. At present, several markers for individual capacity for DNA repair (rs159153 in the *hOGG1* gene (coding for a glycosylase responsible for removal of oxidized bases from DNA); rs3135974 in the *LIG3* gene (coding for ligase III that is responsible for end joining in the late stages of repair by more than one mechanism); rs3219463 and rs3219476 in the *MUTYH* gene (coding for A/G mispair-specific adenine DNA glycosylase); rs6844176 in the *RFC-1* gene (coding for a component of the BRCA1-associated genome surveillance complex that scans DNA for the presence of damage) and the rs41376448 in the *HMGB1* gene (coding for HMGB1, a master regulator of transcription and DNA repair)) have been linked to the risk of acute and chronic GVHD and other causes of transplant-related mortality [22–24].

In patients with transplantations of HPSCs, there is always a risk of recurrence of the original tumour and for development of secondary malignancies, the risk being slightly higher in patients that have received autologous grafts [9]. There is already a report that grafts carrying variant alleles of genes coding for proteins of DNA repair (specifically, the rs1052559 polymorphism in the *XPD* (*ERCC2*) gene and rs861539 in the *XRCC3* gene) may be associated with higher risk of development of secondary leukemia [25].

Studies carried out in mouse models show that downregulation of the capacity for repair of double-strand breaks (DSBs) in DNA decreased the capacity for engraftment of HPSC [26–28]. The effect was observed with several key proteins of double-strand break repair (*Lig4*, *Ku80*, *Exo1*) and was noted to become significant with in vitro aging of the cells in the graft. This 'aging effect' is a hallmark of subtle genetic deficiencies of DNA repair/management of genomic integrity [17].

Role of individual repair capacity for research and potential clinical applications involving stem cells other than HPSC

The data about the role of individual capacity for repair of DNA/maintenance of genomic integrity for the outcomes of transplantations of stem cells other than HPSCs are still sparse. Presently, mesenchymal stem cells (MSCs) are viewed as another potential source of stem cells for transplantation purposes. Bone marrow MSCs may be induced to differentiate to produce several different types of specialized cells, including osteocytes, chondrocytes, adipocytes and endothelial cells [29]. MSCs from Wharton's jelly of the umbilical cord and from placenta are believed to be pluripotent [30]. Multipotent bone marrow MSCs have been shown to be relatively resistant to DNA damage inflicted by inhibition of topoisomerases [31]. Studies using ex vivo expanded MSCs, however, showed that the efficiency of repair of double-strand breaks in DNA tends to decline after repeated passaging [32]. To date, freshly isolated or expanded ex vivo autologous MSCs from bone marrow have been used in experimental therapy of human patients with stroke and spinal cord injury [33]. Assessment of long-term adverse effects was carried out for the latter study and was reported as negative [34]. Nevertheless, the number of in vivo studies of safety of transplantation of MSCs does not permit reliable assessment of the potential risks.hESCs have been (and still are) a 'gold standard' in studies using human pluripotent cells but increased use of human induced pluripotent stem cells (iPSCs) lines has been recently reported [35]. According to the Human Pluripotent Stem Cell Registry (https://hpscreg.eu/news/single_news?id =72; retrieved 2018 Apr 11), nearly 2500 human pluripotent stem cell lines (over 700 hESC lines and about 1800 iPSC lines) are presently listed as globally available. iPSCs have been intensely studied with regard to their potential applications for the reparative and regenerative medicine. Their use was initially limited to research purposes only for a variety of reasons, including 'incomplete' reprogramming (iPSC continue to express genes typical of the cell type that they were derived from); 'cancer-like' expression profile, accelerated aging, low survival and lower efficiency of differentiation [36–38]. Recently, potential future clinical applications have begun to emerge for iPSCs as well as ESCs, including age-related macular degeneration (AMD), vascular disease, diabetes and Parkinson's disease [39–42]. It was demonstrated that human iPSCs deficient for the *LIG4* gene (coding for the main ligase of repair of DSBs by non-homologous end joining (NHEJ)) exhibited significant decrease in reprogramming efficiency than iPSC derived from normal human cells and rapidly accumulated chromosomal abnormalities [43]. Targeted differentiation of these *LIG4*-deficient iPSCs into haematopoietic progenitors was impaired, resulting in accumulation of DSBs and high rates of apoptosis. Later, it was shown that iPSCs without apparent genetic defects subjected to prolonged in vitro passaging

accumulated DSBs and exhibited mitochondrial dysfunction, increased rates of apoptosis and decreased differentiation efficiency [44,45]. Apparently, DNA repair is an important factor for maintenance of stemness qualities of iPSC. iPSCs derived by more recent modified methods were reported to resemble ESCs more than iPSCs derived by traditional methods [46]. Among the main differences were increased capacity for repair of double-strand breaks and increased accuracy of NHEJ for iPSCs derived by improved methodology, therefore, the safety of iPSC preparations in terms of DNA repair capacity has apparently been improved. Nevertheless, other safety concerns might arise. These are related to the fact that there is always an inherent risk that iPSCs derived from the patient's own cells may exhibit, in the course of their establishment or in vitro propagation, a propensity for genetic instability. Since carriership of polymorphisms in genes coding for proteins directly or indirectly responsible for the maintenance of genomic integrity is not uncommon, this risk may be significant when using autologous cells. Already, there has been one suspended trial of treatment of human disease with iPSCs after discovering that the autologous iPSCs intended to be used for treatment of AMD has sustained potentially dangerous mutations [47]. Consequently, designated acts regarding the safety of stem cell preparations have been introduced (the Act on the Safety of Regenerative Medicine (2014) in Japan, where the trial was conducted, and the 21st Century Cures Act in the USA (2016). The trials were only recently resumed after the project leader Masayo Takahashi and the Nobel laureate for 2012 Shinya Yamanaka declared that the cells used further in the project will be provided by the cell bank of Kyoto University's Center for iPSC Cell Research and Application (headed by Yamanaka) in order to guarantee that they have been comprehensively characterized and tested for quality. A list of recommendations regarding future trials using iPSCs have been made, including specific recommendations for the assessment of potential risks; the choices and decisions of the participants free of therapeutic misconception and individualized care for the patients participating in the trial [48]. Nevertheless, the eye is a relatively immunoprivileged site. Potential uses of autologous iPSCs for derivation of differentiated cells and tissues for other than ophthalmological purposes may be limited by histocompatibility issues. Recently, several clinical trials for potential uses of iPSCs in neurological disease have been launched [49,50] but no results have been reported yet. Assessment of the individual capacity for DNA repair/maintenance of genomic integrity may assist in the screening of potential patients to differentiate between patients that may be eligible for transplantations of autologous iPSC-derived cells and patients that may benefit from cell preparations from allogeneic iPSCs.

Reports about the role of the capacity for repair of DNA damage/maintenance of genomic integrity in ESCs are still quite rare in the specialized literature. The intact functioning of the mechanism for repair of DNA is of prime importance for ESCs, as their restriction point of the cell cycle is weak (in human ESCs) or virtually non-existent (in murine ESCs) [11–13]. Repair of DSBs in ESCs is important, as with all types of stem cells. This may be especially valid for repair by homologous recombination, as it was shown to be used as a preferred repair pathway throughout the cell cycle, at least in murine ESCs [51]. It has been recently demonstrated that the XPC-HR23B complex (normally responsible for the identification of genomic damage in untranscribed regions) may play a role in the control of the 'stemness' state in human hESCs [52,53]. This was implemented by activation of transcription of OCT4 and SOX2 and by regulation of demethylation of DNA via rapid excision-synthesis-end ligation cycle that generated methylation-free DNA regions faster than the 'conventional' thymine-DNA glycosylase-mediated base excision repair. Differentiation of ESCs into specialized cell types may be dependent on the efficiency of specific types of DNA repair. Specifically, differentiation along the myogenic line in human ESCs requires temporal stimulation of the DNA repair mediated by XRCC1 (a stabilizing factor of DNA ligase III) [54].

Only recently, it has been reported that China was on the verge of launching the first ever clinical trial for use of hESC-derived cell products in treatment of Parkinson's disease [55]. It is still too early for any results, but nevertheless, it could be expected that the potential safety concerns would be, at least partly, related to genomic change occurring in the process of cell maintenance in vitro.

Apparently, the efficiency of repair of DNA damage is an important factor for maintenance of stem cells in culture, for efficient reprogramming back to pluripotent state and for differentiation into specific cell types. It could be expected that subtle deficiencies of DNA repair/maintenance of genomic integrity may affect the survival of stem cells in culture, especially with increased passaging. Moreover, even for the stem cell preparations prepared in strict xeno-free conditions, the contact with agents with potentially

genotoxic effects such as DMSO (dimethyl sulphoxide) is, at present, unavoidable. Only a limited number of studies about the role of subtle variations of individual repair capacity in the maintenance of stem cell lines in vitro are currently available [56,57]. Since the applications of stem cells and stem cell-derived products continue to expand and diversify, it might be advisable to augment the currently existing panel of markers used for characterization of stem cells and stem cell lines with markers for individual repair capacity in order to improve the process of selection for lines with potential use in clinical applications.

Conclusions

Knowledge about the individual DNA repair capacity of human stem cell lines may be valuable for the purposes of research, especially in light of potential genotype–phenotype correlations. Use of cells and cell lines with capacity to repair genotoxic damage that is inferior to the average may be undesirable for potential clinical applications because of higher risks of engraftment failure and/or potential long-term complications. Analysis of individual capacity for repair of genotoxic damage/maintenance of genomic integrity may become a tool in the assessment of the capacity for proliferation and differentiation of human stem cell lines with regard to their potential long-term maintenance in vitro and the potential in vivo applications.

Disclosure Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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